

## **REMARKS**

### **Status of the claims and formal matters**

Claims 66-95, 97-100, 102-109, 111-116, 118, 119, 122-124, 126, 127, and 133-141 are pending in the instant application. Claims 68-86, 95, 97-100, 102-109, 111-116, 118, 119, 122-124, 126, and 127 were previously withdrawn from consideration. Claims 66, 67, 87-94, 133-137, and 139-141 stand rejected by the Patent Office.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner.

### **Specification**

The Examiner objects to the disclosure for certain trademark iterations. (Office Action, p. 3) Applicant believes the cited trademarks of Qiaquik, Zymoclean, and Synergel are properly capitalized but would appreciate any further comment. The specification has been amended as per page 2, above, to address the instant objection.

### **Double patenting**

1. Claims 66, 67, 87, 88, 90, 94, 133, 134, and 136-141 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 25-28 of copending U.S. Patent Application No. 11/622,359. Abeyance of the double patenting rejection of claims 66, 67, 87, 88, 90, 94, 133, 134, and 136-141 is requested.

It remains unknown what subject matter claimed and disclosed in the present application will be deemed allowable. Hence, any statement regarding this rejection made on Applicants' behalf would be premature. Therefore, Applicants respectfully traverse this rejection and request that it be held in abeyance until subject matter is deemed allowable in this application.

2. Claims 66, 67, 87, 88, 90, 93, 94, 133, 134, 136, 137, and 139-141 are rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 29, 31, 33, 37, and 42 of U.S. Patent No. 6,632,671. Abeyance of

the double patenting rejection of claims 66, 67, 87, 88, 90, 93, 94, 133, 134, 136, 137, and 139-141 is requested.

It remains unknown what subject matter claimed and disclosed in the present application will be deemed allowable. Hence, any statement regarding this rejection made on Applicants' behalf would be premature. Therefore, Applicants respectfully traverse this rejection and request that it be held in abeyance until subject matter is deemed allowable in this application.

### **103 Rejections**

The Examiner has raised a number of objections under 35 U.S.C. §103. Applicant has earnestly endeavored to address these objections in the remarks below. In particular, Applicant addresses the key references cited by the Examiner, i.e., the references of Ueda et al. (primary), Landry et al., and Kondo et al., and the references of Matsuzawa et al. (primary) and Levy et al. Applicant's remarks that follow are directed primarily to these references and less so to other secondary and tertiary references. The Applicant's previously submitted remarks are incorporated herein by reference in their entirety.

Before addressing the instant rejections, Applicant would like to reiterate several key features of the claimed invention.

### **The invention**

The claimed invention comprises a surfactant micelle comprising a therapeutic bioactive component and a hydrophobic surfactant, with a surrounding shell comprising a polypeptide ligand and Li<sup>+</sup>, which results in a nanocapsule of less than 50 nanometers in diameter capable of receptor-mediated targeting and uptake into the cell. As submitted previously, the claimed invention provides the first mechanically-stabilized sub-50 nm targeted particle encapsulating a therapeutic bioactive component, a particle that the prior art lacked and that provides unexpected benefits.

The ultrasmall size of the claimed composition is enabled, in part, by the formation of the core by a transiently stable hydrophobic micelle; stabilization and targeting are efficiently provided by the polypeptide shell. As likewise previously submitted, the problems that are simultaneously addressed by the claimed invention include, for example,

delivery of a therapeutic agent intact into the cell, by protecting the agent from enzymatic degradation and by avoiding lysosomal degradation, in a cell-targeted manner.

### **Prosecution history**

The non-final Office Action and accompanying §103 Rejections dated March 31, 2011, constitutes a new, third set of §103 Rejections and associated new art citations for essentially the same subject matter, since prosecution was reopened in July 2009 following Applicant's pre-appeal of Examiner's §102 and 103 Rejections. The record shows the Examiner has repeatedly moved from one set of references to a new set in response to Applicant's remarks regarding the inappropriateness of the immediately-prior set of rejections. This prosecution history is clearly non-compliant with the MPEP's requirements for completeness of examination and compact prosecution<sup>1</sup>. Below, Applicant has endeavored to address the new concerns raised by the Examiner and earnestly hopes that this will be the last set of new references Applicant must address in placing the application in condition for allowance.

#### **A. Rejection of claims 66, 67, 87-89, 93, 135, 137, and 139**

The Examiner has rejected claims 66, 67, 87-89, 93, 135, 137, and 139 under 35 U.S.C. § 103(a) as being unpatentable over Ueda, et al. (1997 *J Microencapsulation* 14:593-605) in view of each of Landry, et al. (1996 *Biomaterials* 17:715-723), Ghitescu, et al. (1986 *J Cell Biol* 102:1304-1311), Kondo, et al. (1991 *Anal Biochem* 198:3035, abst), and Boulikas (US 6,030,956). The Applicant traverses this rejection.

##### **A.1. Rejection of independent claim no. 66 over primary reference Ueda et al.**

In Examiner's rejection of the claim no. 66, Ueda as the primary reference is cited as teaching nanoparticles comprising PVA, PLA, loperamide (a bioactive compound) and a surfactant which has an HLB of less than 6.0 (for example, sorbitan monosterarate with HLB of 4.7; see Table 4), with the smallest disclosed size being 164 nanometers (Table 1). Applicant notes Ueda does not teach several elements of independent claim no. 66 of the instant invention, including a polypeptide shell, a lithium cation, or sub-50 nanometer size.

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<sup>1</sup> See MPEP § 706.07 and 707(a), and 2106(II).

As noted, the smallest particle size disclosed by Ueda is 164 nanometers, and this is a sub-optimal configuration as the particles were produced with operating pressure at 800 mbar, a level that yields markedly lower entrapment efficiency than lower operating pressure. For comparison, Ueda reports particles produced at the preferred level of 200 mbar, are 211 nanometers in diameter. (Table 1 and p. 598)

Examiner modifies Ueda with Landry to obtain nanoparticles with a polypeptide (albumin) shell (Office Action, p. 9). Examiner states that because Landry's nanoparticles are formed by the same solvent-evaporation technique as Ueda, it would have been obvious to modify the method of Ueda by replacing PVA with albumin to achieve the predictable result of obtaining cell-targeted, drug loaded nanoparticles. Landry reports nanoparticle size of 100 nanometers in diameter. Similar to Ueda, Landry does not teach several elements of independent claim no. 66 of the instant invention – i.e., a therapeutic bioactive component, a hydrophobic surfactant, a lithium cation, and sub-50 nm size.

Examiner modifies Ueda and Landry with Kondo to obtain a particle protein shell comprising Li<sup>+</sup>, stating Ueda teaches that a precipitated shell enhances drug entrapment, and that Kondo illustrates that precipitating proteins was routine in the prior art. (Office Action, p. 9) Kondo does not teach use of Li<sup>+</sup> with nanoparticles.

Examiner states that Ueda, Landry, and Kondo do not teach a particle of 50 nanometers in diameter, as claimed in claim no. 66. Examiner notes, however, that the references do teach “that particle size can be optimized by varying parameters such as the homogenization conditions, PLA and albumin concentrations, or PLA and albumin molecular weight”. (Office Action, p. 10)

#### **A.1.a. Failure to identify result-effective variable to routinely achieve sub-50 nm size**

Examiner states Ueda, Landry and Kondo do not teach a particle size of 50 nanometers in diameter, but they do teach particle size can be “optimized” by varying parameters such as homogenization conditions, PLA and albumin concentrations, or PLA and albumin molecular weight. (Office Action, p. 10) As noted in the Office Action, Applicant previously argued that none of the optimization methods described in Ueda were identified to produce a particle size of less than about 164 nanometers. Examiner replies that Applicant only identified “which conditions result in larger particle size and which

conditions result in smaller particle size”, that Applicant’s statements were incomplete because Ueda teaches other variables that “influence” particle size, and that “one of skill in the art would know what parameters to vary such as to decrease the particle size.” (Office Action, pp. 12-13) Applicant submits Examiner’s conclusions regarding the implied routine nature of achieving the sub-50 nanometer size of the instant invention do not support a *prima facie* finding of obviousness, in view of MPEP examination requirements, and should be withdrawn.

Section 2141.05 of MPEP relates to obviousness of ranges, and Section 2141.05(II) relates to optimization of ranges. Section 2141.05(II)B states that “[a] particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation”. In the instant prosecution, the Examiner simply lists a handful of possible parameters from Ueda that “influence” particle size, and defers to one of skill in the art to know which parameters to vary in order to *decrease* size. Further, even if the Examiner had identified which parameters of primary reference Ueda to vary, and how, in order to reduce particle size, there is still the unaddressed issue of identifying what the art-recognized result of varying those parameters would be. Identifying the art-recognized result is essential to determining whether sub-50 nanometer size could be achieved through routine experimentation. Thus, an art-recognized result would not be just a general assertion of “particle size-reduction”, but rather a more specific statement of the minimum size that a particle, similar in composition to the claimed nanocapsule, can be reduced to after varying a given parameter in a certain manner, as known in the art.

While Applicant does not concede that Ueda teaches a particle similar in composition to the claimed nanocapsule, the following example is provided to illustrate the relevance of recognized results to this prosecution. As described above, Ueda has identified various size-optimizing parameters, with the smallest nanoparticle disclosed being 164 nanometers (211 nanometers with optimal drug entrapment). Applicant submits one of skill in the art would not consider this recognized result, which is more than 3x the size of the claimed nanocapsules, to support Examiner’s conclusion that Ueda teaches parameters that can be routinely modified to achieve a sub-50 nanometer particle.

Examiner also asserts Landry teaches what parameters “influence” the size of the particles, and that “[i]mportantly, Landry teaches nanoparticles of 100 nanometers (i.e., below 164 nanometers)”. (Office Action, pp. 10 and 13) Examiner refers to Landry p. 716, column 2, first and second paragraphs. Applicant respectfully repeats its argument from the Reply of December 22, 2010, that Examiner’s cited passage from Landry does nothing more than describe the emulsification-solvent evaporation method of Landry’s nanoparticles, and provides no teaching whatsoever as to what parameters might be varied to influence particle size, much less to reduce particle size to sub-50 nanometers. Further, Examiner provides no rational underpinning as to why Landry’s teaching of nanoparticles of 100 nanometers would be transferable to the primary reference Ueda nanoparticles as modified by Landry, including consideration of their different compositions (e.g., Ueda particles include a hydrophobic surfactant, but Landry’s do not). Applicant submits one of skill in the art would focus first on the teachings of the primary reference Ueda, and would not view Landry as teaching that Ueda’s surfactant-comprising composition can be modified to obtain a size of 100 nanometers, or that Landry teaches the use of any parameter to effectively reduce particle size, much less to reduce to sub-50 nanometer size through routine experimentation.

Applicant therefore submits Examiner has failed to demonstrate that the sub-50 nanometer size of the claimed nanocapsules could be obtained by varying specific parameters through routine experimentation as guided by the references, and as such, has not established a *prima facie* showing of obviousness.

**A.1.b. No motivation or reasonable expectation of success to modify the reference particles with Kondo**

Regarding Examiner’s use of Kondo to modify the particles of Ueda as modified by Landry in order to obtain particles with a Li<sup>+</sup>-based shell, Examiner cites as motivation Ueda’s teaching that a precipitated shell enhances drug entrapment, describes use of Li<sup>+</sup> to precipitate proteins as “routine in the prior art”, and states that it would have been obvious “to further precipitate the protein coat (of Ueda and Landry) with Li<sup>+</sup>, with a reasonable expectation for success”. (Office Action, pp. 9-10) Applicant respectfully disagrees with respect to the asserted motivation and likelihood of success, as discussed further below.

Applicant has previously argued that Kondo does not serve as motivation to modify nanoparticles with Li<sup>+</sup>, because Kondo is not related to precipitating nanoparticles. Examiner's reply is that such an argument is not persuasive because Kondo does not have to teach each and every claim limitation and that, because the art teaches that protein shells in nanoparticles could be precipitated with cations such as Ca<sup>2+</sup>, Ba<sup>2+</sup>, Gd<sup>2+</sup>, Ni<sup>2+</sup>, Al<sup>2+</sup>, and Mn<sup>2+</sup>, "one of skill in the art would know that any protein-precipitating agent, including the cations taught by the prior art, would work". (Office Action, pp. 13-15) Applicant does not dispute that Kondo need not teach every claim limitation, or that other cations were known to be useful for particle precipitation, but submits the problem Kondo is solving with the use of lithium has nothing to do with nanoparticle formulation, that the particle-precipitating cations known in the art were distinctly different from Li<sup>+</sup>, and that the Examiner has relied solely upon the instant application to conclude as obvious the incorporation of Li<sup>+</sup> as a cation in nanoparticles.

The problem Kondo addresses is purifying plasmid DNA preparations so they can be employed in molecular cloning and sequencing. Kondo describes a process that treats crude plasmid DNA preparations with lithium chloride and ethidium bromide, as being able to "dehydrate and deproteinize crude plasmid DNA samples, lowering the solubility of RNAs, liberating proteins, and finally precipitating all the RNA and proteins that contaminate DNA preparations..." (p. 34) Thus, Kondo teaches the use of lithium chloride and ethidium bromide to *separate* DNA from protein (and RNA). Kondo's teaching that Li<sup>+</sup> may be useful for precipitation (separation) of RNA and proteins from DNA preparations, would not render obvious the instant invention's inclusion of Li<sup>+</sup> in the polypeptide shell surrounding the claimed hydrophobic surfactant micelle. Applicant submits the ordinary artisan seeking to form precipitated particles, would have looked to known *particle-precipitating* cations, which are multivalent (see below), to form precipitated particles, and would have no need or motivation to look to the unrelated teachings of Kondo and use Li<sup>+</sup>, which is monovalent, for that purpose.

Examiner cites Magdassi as exemplifying use of cations to precipitate protein shell nanoparticles. (Office Action, p.15) Applicant submits Magdassi teaches use of *multivalent* cations to formulate stable submicron protein particles (e.g., Abstract, p.1). Magdassi teaches a benefit of using multivalent cations is that it allows linking of

negatively charged molecules, such as DNA, to the negatively charged protein (e.g., Abstract). One of skill in the art would understand Li<sup>+</sup> is a monovalent ion not capable of such linking, and is not only not taught nor suggested by Magdassi, but would not present a reasonable expectation for success should it be explored. The artisan would further understand that Magdassi's teaching of multivalent cations to link DNA and protein in nanoparticle formulations, directly contrasts with Kondo's teaching of Li<sup>+</sup> to separate DNA and protein in plasmid DNA preparations, and that the use of Li<sup>+</sup> to precipitate nanoparticles would therefore not have a reasonable chance of success.

Applicant therefore submits Examiner has impermissibly relied upon hindsight, using the teachings of the instant invention and not the motivation of the skilled artisan, to modify the particles of Ueda and Landry with Kondo, and that Kondo does not support a *prima facie* finding of obviousness.

#### **A.2. Rejection of dependent claim nos. 67 and independent claim no. 139<sup>2</sup>**

With respect to the limitation of the bioactive agent being a polynucleotide, Examiner asserts it would have been obvious to the artisan to use the particles taught by the combined teachings above in gene therapy, because the prior art teaches the necessity to use gene therapy to treat diseases such as cancer (referencing Boulikas; Office Action, pp. 10-11).

Applicant submits Examiner's rejection of claim no. 67 is not supported and should be withdrawn. Examiner overlooks that the purpose of Ueda, the primary reference, is to formulate loperamide hydrochloride (LCM) in biodegradable polymeric drug carriers, and to examine the effects of various optimization techniques on properties such as drug entrapment, particle size, and drug release (Abstract). LCM is a lipophilic drug; Ueda teaches that evaporation methods (such as the one Ueda uses) are limited to water-insoluble drugs, because water soluble drugs easily partition into the aqueous phase from the organic phase during emulsification, evaporation, and purification (p. 597). Examiner articulates no reason why one of skill in the art would have a reasonable expectation of success to incorporate a water soluble drug such as a polynucleotide in the particles of Ueda. Applicant submits the teachings of Ueda preclude such expectation. Further, Applicant

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<sup>2</sup> Applicant notes Examiner has referenced only claim no. 67 in making this set of arguments, but by extension believes claim no. 139 would be subject to the same arguments.

submits the secondary references do not overcome those deficiencies. Reconsideration is respectfully requested.

**A.3. Remaining references fail to overcome deficiencies of references discussed above**

It is submitted that the instant rejection fails for independent claim nos. 66 and 139 and dependent claim no. 67 for the reasons identified above, that the instant rejection similarly fails for dependent claim nos. 87-89, 93, 135, and 137, and that Ghitescu and Sheng fail to remedy the deficiencies of the references.

**B. Rejection of claims 66, 67, 87-90, 93, 135-137, and 139**

The Examiner has rejected claims 66, 67, 87-90, 93, 135-137, and 139 under 35 U.S.C. § 103(a) as being unpatentable over Ueda, et al. taken with each of Landry, et al., Ghitescu, et al., Kondo, et al., and Boulikas, in further view of Krishnan et al. (*Colloids Surfaces A: Physiochem Eng. Aspects*, 1999, 149:355-366).

Applicant incorporates by reference the arguments made above in relation to the rejection of claim nos. 66, 67, 87-89, 93, 135, 137, and 139. It is submitted that the instant rejection fails for the reasons identified above, and Krishnan fails to remedy the deficiencies of the references.

**C. New rejection: Claims 66, 67, 87-89, 91-93, 135, 137, and 139**

The Examiner has rejected claims 66, 67, 87-89, 91-93, 135, 137, and 139 under 35 U.S.C. § 103(a) as being unpatentable over Matsuzawa, et al. (1995 *Biol Pharm Bull* 18: 1718-1723) in view of each of Davies, et al. (1987 *J Colloid and Interface Sci* 116:88-99, abst), Levy, et al. (WO96/20698), Chang, et al. (1996 *J Pharmaceutical Sci* 85:13225-13230), and Kondo, et al. (1991 *Anal Biochem* 198:3035, abst). Applicant traverses this rejection.

**C.1. Rejection of independent claim no. 66 over primary reference Matsuzawa et al.**

Matsuzawa discloses nanoparticles comprising insulin (a bioactive compound) and a surfactant which has an HLB of less than 6.0 (for example, Span 80 with an HLB of 4.3). Matsuzawa does not teach several elements of independent claim no. 66 of the instant

invention, including a polypeptide shell for cell targeting, a lithium cation, or sub-50 nanometer size, as discussed below. Examiner combines Matsuzawa with Levy for the targeting polypeptide and the sub-50 nanometer size limitations, and with Kondo for the lithium cation limitation. Applicant submits all of these combinations are in error as discussed below, and that the Examiner has therefore failed to establish a *prima facie* case of obviousness.

For background prior to the discussion below, it is noted Matsuzawa does not disclose any specific dimensions of particle size, nor does the Examiner provide any estimate. Based on the micrographs of the filtered emulsions shown in Fig. 4 of this reference, with gelatin concentration of 5%, Applicant estimates the diameter of Matsuzawa's particles to be between several hundred nanometers and one micron.

#### C.1.a. Levy's co-solvent system is not suitable to modify the particles of Matsuzawa

Examiner asserts that Levy's co-solvent system, purportedly capable of producing ultrasmall particles, applies to formulation methods that include w/o/w emulsions (Office Action, pp. 23-24), such as the w/o/w emulsion of primary reference Matsuzawa. Applicant respectfully does not agree that Levy's co-solvent system applies to w/o/w emulsions, and submits the co-solvent system is not suitable to modify the particles taught by Matsuzawa.

Importantly, Levy discloses particles of 20-35 nanometer size *only* with respect to the co-solvent system, as described in Example 6 ("[U]ltrasmall particles are formed in accordance with the principles of the invention by a technique using a co-solvent system.....Ultrasmall particles are defined herein as having a mean diameter of between about 10 nm to 50 nm, and more preferably 20 nm to 35 nm.") As described in Example 6, Levy's co-solvent system entails dissolving the bioactive agent into a system of two solvents, such as dichloromethane and dimethylacetamide, to comprise an organic phase, and then emulsifying the organic phase in an aqueous phase. The artisan would recognize that this (o-o)/w emulsion is not compatible with the w/o/w emulsion of Matsuzawa ,which comprises PBS, soybean oil, and water (pp. 1718-1719). For example, the insulin cargo of Matsuzawa would not survive dissolution in an organic co-solvent phase such as described by Levy. Accordingly, the artisan would be neither motivated to combine the two

methods, nor encouraged to undertake such a combination with a reasonable expectation of success.

At issue is the Examiner's mistaken belief that Levy teaches use of the co-solvent system for w/o/w emulsions. (Office Action, p. 23) Examiner supports this belief by citing Levy p. 18, lines 8-15 "for incorporation of hydrophilic agents into w/o/w emulsions" and comparing this passage "with the co-solvent system disclosed in Example 6". (Office Action, p. 24) With respect first to the passage on p. 18 of Levy, Applicant agrees it indeed describes the co-solvent system, but points out the description is actually an (o-o)/w emulsion, not a w/o/w emulsion as indicated by the Examiner. More specifically, the co-solvent process for hydrophilic agents as described on p. 18 of Levy entails dissolving a polymer in a nonpolar organic solvent, and dissolving a hydrophilic bioactive agent in a semipolar organic solvent. The organic solutions are then combined into a single organic phase incorporating both the polymer and the hydrophilic bioactive agent. The organic phase is then emulsified in an aqueous solution of an emulsifying agent. Thus, Levy defines the co-solvent system for hydrophilic agents in terms of an (o-o)/w emulsion, not a w/o/w emulsion as asserted by the Examiner.

With respect to Examiner's statement regarding hydrophilic agents and the co-solvent system disclosed in Example 6, the only reference to hydrophilic agents in Levy's prophetic Example 6 is in the last paragraph, which reads as follows:

While Example 6 is directed to making ultrasmall particles incorporating a hydrophobic agent, the technique is applicable to hydrophilic agents. A multiple emulsion system (water-in-oil-in-water), similar to Example 5, may be used wherein the bioactive agent is dissolved in the aqueous phase.

Applicant submits the phrase "the technique is applicable to hydrophilic agents" refers to the co-solvent technique, and that technique as it relates to hydrophilic agents is specifically described on p. 18, lines 8-15 of Levy (as Examiner pointed out). As discussed above, the described technique is an (o-o)/w emulsion. Importantly, Levy next teaches the co-solvent technique is not suitable for all hydrophilic agents; thus, the second sentence of the paragraph from Example 6, "A multiple emulsion system (w/o/w), similar to Example 5, may be used wherein the bioactive agent is dissolve in the aqueous phase" refers to

*solvent-sensitive* hydrophilic agents that cannot be formulated via the co-solvent technique, because they cannot withstand dissolution in an organic phase, and therefore must be dissolved in the aqueous phase. Such solvent-sensitive agents include proteins and vaccine antigens (p.19, lines 5-14 of Levy). Thus, the w/o/w emulsions for solvent-sensitive hydrophilic agents such as proteins clearly fall outside of Levy's definition of "co-solvent nanoparticles" and, accordingly, outside of the 20-35 nanometer size defined for co-solvent particles. To ascertain the size of Levy's w/o/w emulsion particles (which potentially may be more comparable with Matsuzawa's w/o/w process, but which Applicant does not concede), the artisan would look to Example 5 as referenced by Levy in the above paragraph, and find a disclosure of 160 nanometers.

Therefore, Levy's co-solvent system purportedly capable of producing ultrasamall, 20-35 nanometer particles can be defined as an (o-o)/w emulsion, whether for hydrophilic or hydrophobic cargo. An (o-o)/w emulsion process such as Levy's is not combinable with a w/o/w process such as Matsuzawa's, and cannot be used to modify Matsuzawa. For example, Matsuzawa's w/o/w emulsion process is directed toward formulating a protein (insulin), a cargo which cannot be dissolved in the organic phase as would be called for in Levy's (o-o)/w co-solvent technique. In view of these disclosures, the artisan would understand that the co-solvent (i.e., (o-o)/w) system of Levy is not suitable for modifying the insulin particles of Matsuzawa produced by w/o/w, including for the purpose of reducing the size of Matsuzawa's several-hundred-nanometer particles to 50 nanometers.

Applicant appreciates the challenges of interpreting an extremely lengthy document such as Levy. However, the Examiner has mistakenly interpreted the teachings of Levy by concluding that the co-solvent system comprises w/o/w emulsions, and mistakenly implied that the insulin cargo of primary reference Matsuzawa could be formulated in Levy's co-solvent system, to support the contention that Matsuzawa's several-hundred-nanometer particles can be reduced to 50 nanometers through routine experimentation. Consequently, the Examiner has not discharged the initial burden of establishing a *prima facie* case of the subject claims, and withdrawal of these objections is therefore respectfully requested.

**C.1.b. No motivation or reasonable expectation of success to modify the reference particles with Kondo**

Examiner's combination of Kondo with the reference particles of Matsuzawa is in error, for the same reasons as those described in section A.1.b., above, which are hereby incorporated by reference.

**C.2. Remaining references fail to overcome deficiencies of references discussed above**

It is submitted that the instant rejection fails for independent claim no. 66 over primary reference Matsuzawa for the reasons identified above, that the instant rejection similarly fails for independent claim no. 139 and dependent claim nos. 67, 87-89, 91-93, 135, and 137, and that Davies and Chang fail to remedy the deficiencies of the references.

**D. Rejection of claims 66, 67, 87-89, 91-93, 133-135, 137, and 139-141**

The Examiner has rejected claims 66, 67, 87-89, 91-93, 133-135, 137, and 139-141 under 35 U.S.C. § 103(a) as being unpatentable over Matsuzawa, et al. (1995 *Biol Pharm Bull* 18: 1718-1723) taken with each of Davies, et al. (1987 *J Colloid and Interface Sci* 116:88-99, abstract), Levy, et al. (WO96/20698), Chang, et al. (1996 *J Pharmaceutical Sci* 85:13225-13230), and Kondo, et al. (1991 *Anal Biochem* 198:3035, abstract), in further view of Schneider, et al. (1998 *FEBS Letters* 429:269-273).

Applicant incorporates by reference the arguments made above in relation to the rejection of claims 66, 67, 87-89, 91-93, 135, 137, and 139. It is submitted that the instant rejection fails for the reasons identified above, and Schneider fails to remedy the deficiencies of the references.

**E. Rejection of claims 66, 67, 87-89, 91-94, 135, 137, and 139**

The Examiner has rejected claims 66, 67, 87-89, 91-94, 135, 137, and 139 under 35 U.S.C. § 103(a) as being unpatentable over Matsuzawa, et al. taken with each of Davies, et al., Levy, et al., Chang, et al., and Kondo, et al., in further view of Magdassi et al.

Applicant incorporates by reference the arguments made above in relation to the rejection of claims 66, 67, 87-89, 91-93, 135, 137, and 139. It is submitted that the instant rejection fails for the reasons identified above.

**F. Rejection of claims 66, 67, 87-93, 135, 137, and 139**

The Examiner has rejected claims 66, 67, 87-89, 91-93, 135, 137, and 139 under 35 U.S.C. § 103(a) as being unpatentable over Matsuzawa, et al. taken with each of Davies, et al., Levy, et al., Chang, et al., and Kondo, et al., in further view of Krishnan et al.

Applicant incorporates by reference the arguments made above in relation to the rejection of claims 66, 67, 87-89, 91-93, 135, 137, and 139. It is submitted that the instant rejection fails for the reasons identified above.

**G. Rejection of claims 66, 67, 87-89, 93, 94, 135-137, and 139**

The Examiner has rejected claims 66, 67, 87-89, 93, 94, 135-137, and 139 under 35 U.S.C. § 103(a) as being unpatentable over Ueda, et al. taken with each of Landry, et al., Ghitescu, et al., Kondo, et al., and Boulikas, in further view of Magdassi et al.

Applicant incorporates by reference the arguments made above in relation to the rejection of claims 66, 67, 87-89, 93, 135, 137, and 139. It is submitted that the instant rejection fails for the reasons identified above.

**H. Prior art not relied upon**

The Examiner makes of record and refers to, but does not rely upon, Bazile et al. (1992 *Biomaterials* 13:1093-1102) to "demonstrate that albumin-coated nanoparticles with different sizes, including 50 nanometer nanoparticles, can be successfully obtained". Office Action, p. 30. There is no evidence in Bazile that 50 nanometer particles of any type were produced by the authors. The Examiner appears to be making this assertion based on a single sentence, at p. 1094 of the reference, that the paper "describes the fabrication of 50-500 nm PLA nanoparticles coated with albumin." A careful review of the reference shows instead, however, that the paper does not report preparation of 50 nanometer particles. Indeed, the Abstract recites "PLA nanoparticles (90-250 nanometers) were prepared", and Figs. 1 and 2 of the reference show the minimum particle size to be approximately 90 nanometers in diameter. Further, the reference does not describe, and the Examiner was apparently unable to identify, a result-effective variable that could be routinely varied to produce particles smaller than 90 nanometers. Last, Applicant notes for

the record that the particles of Bazile are even further removed from the claimed 50 nanometer capsule composition, in that the reported particles do not incorporate a therapeutic bioactive component, a hydrophobic surfactant, or a Li<sup>+</sup> cation.

Applicant can provide additional remarks regarding why Bazile, alone or in combination with the other references cited by the Examiner, would not have rendered the instant invention obvious. For efficient prosecution, however, and as the reference is not relied upon by the Examiner, Applicant invites the Examiner to call the undersigned at the number provided should further discussion appear necessary to address the Examiner's concerns.

## CONCLUSION

For the reasons set forth above, Applicant respectfully submits that the claims as filed and as presented herewith are allowable over the art of record, and reconsideration and issuance of a Notice of Allowance are respectfully requested. Should it be considered helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for a three-month extension of time pursuant to 37 C.F.R. § 1.136(a). A check for the appropriate fee is enclosed.

Respectfully submitted,

Date: September 29, 2011

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